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In This Issue

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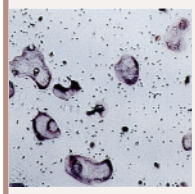
Prostaglandins and osteoclast maturation

(See article on pages 823–832.)

Here, Okada and co-workers explore a well-established but poorly understood effect of the prostaglandin PGE_2 on the development of bone resorbing osteoclasts. Osteoblast precursors can complete their differentiation in organ culture if they are co-cultured with and allowed to contact osteoblasts. Prostaglandins promote this differentiation, and inhibitors of prostaglandin synthesis, such as the non-steroidal anti-inflammatory drugs, diminish osteoclast differentiation in culture. Based on both the biochemical specificity of these inhibitors and genetic studies using mice lacking one of the two prostaglandin G/H synthase genes, *PGHS-1* or *-2*, it appears that only PSGH-2 and its product PGE_2 are required in this process. Indeed, Okada et al. determine that PGE_2 can be limiting for osteoclast formation in this system. When treated to induce osteoclasts, bone marrow cells cultured from *PSGH-2*$^{+/-}$ heterozygous animals produce approximately half as many osteoclast-like cells as do *PSGH-2*$^{+/+}$ cultures, and PGE_2 levels in the medium are reduced by a corresponding amount. Osteoclast formation in *PSGH-2*$^{-/-}$ cultures, in which PGE_2 levels are nearly undetectable, is rarer still, but exogenous PGE_2 restores osteoclast formation to maximal efficiency in cultures of any PSGH-2 genotype. By co-culturing osteoclast precursors and osteoblasts from different genotypes, the authors show that prostaglandin synthesis is required in the latter cells but not the former. The effects of PGE_2 in this system may be mediated by expression of the RANK ligand, a known inducer of osteoclast formation whose mRNA is reduced 2-fold in *PSGH-2*$^{-/-}$ osteoblasts cells.



Quelling immune responses after a viral infection

(See article on pages 813–821.)

In the wake of a systemic viral infection, T and B lymphocytes specific for the virus undergo apoptosis and are cleared from peripheral organs. The importance of this activation-induced cell death (AICD) is evident from the phenotype of mice lacking Fas or Fas ligand (FasL), crucial mediators of immune cell apoptosis. Such mice mount an efficient reaction to murine cytomegalovirus (MCMV), but they show persistent inflammation and autoimmune reactivity in their lungs and livers long after the virus is cleared. Here, Zhang and colleagues follow up on evidence that antigen presenting cells (APCs) expressing FasL can induce tolerance to specific antigens, showing $FasL^+$ APCs suffice to direct AICD, even in animals that otherwise lack FasL. When these APCs are pulsed with MCMV in culture and then introduced intravenously into FasL-deficient animals, they present the viral epitopes, promote AICD, and suppress inflammation more vigorously than other $FasL^+$ macrophages. Although their anti-inflammatory effect is seen in the peripheral organs, these reintroduced lymphocytes home directly to the marginal zone of the spleen. Evidently, ongoing inflammation requires a constant supply of T-cells, and FasL expression by APCs allows the killing of newly emerging splenic T cells.